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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 221/18, C07C 215/64, 217/74, A61K 31/44, 31/135

A1

(11) International Publication Number: WO 97/30977

(43) International Publication Date: 28 August 1997 (28.08.97)

(21) International Application Number: PCT/US97/02620

(22) International Filing Date: 19 February 1997 (19.02.97)

(30) Priority Data:
08/606,393 23 February 1996 (23.02.96) US

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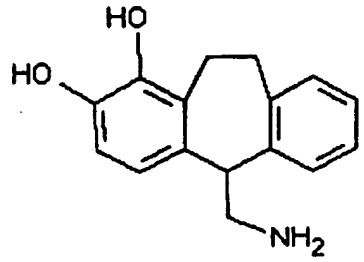
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
*With international search report.*

(54) Title: SELECTIVE D1 DOPAMINE RECEPTOR AGONISTS AND PARTIAL AGONISTS/ANTAGONISTS

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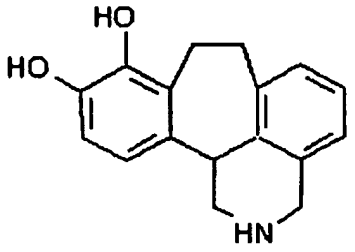


(2)

(57) Abstract

Disclosed are compounds (1) and (2), and derivatives and analogs thereof, which are agonists for the D1 dopamine receptor. These compounds can be used to treat an individual with Parkinson's disease. Also disclosed are monohydroxy analogs of compounds (1) and (2), and derivatives and analogs thereof, which are partial D1 agonists or antagonists. These compounds can be used to treat an individual who abuses cocaine.

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# SELECTIVE D1 DOPAMINE RECEPTOR AGONISTS AND PARTIAL AGONISTS/ANTAGONISTS

## Background

Parkinson's disease is characterized by the progressive death of presynaptic dopamine neurons in the substantia nigra that innervate postsynaptic striatal neurons and a resultant loss of striatal dopamine (Cedarbaum and Schleifer, "Drugs for Parkinson's disease, spasticity and acute muscle spasms", in Goodman and Gilman's The Pharmacological Basis of Therapeutics, A.G. Goodman, T.W. Rall, A.S. Nies and P. Taylor, eds. Eighth Edition, McGraw Hill, pp. 463-484 (1992)). The primary therapy for Parkinson's disease involves compensating for the loss of dopamine in the striatum. The most commonly administered drug for the treatment of Parkinson's disease is levodopa, which is converted into dopamine in the central nervous system. However, levodopa can cause severe side effects such as nausea, vomiting, cardiac arrhythmias and hypotension. Long-term use of levodopa can result in abnormal involuntary movements and psychosis. Consequently, there is a need for new treatments for Parkinson's disease.

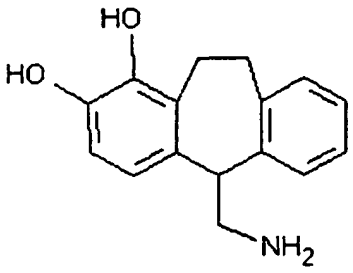
Dopaminergic receptors have also been implicated in cocaine abuse. Specifically, cocaine is thought to block the reuptake of dopamine into dopamine-releasing neurons; as a consequence, dopamine levels can return to normal in the chronic presence of cocaine and be depleted in its absence. Subsequent reduced levels of synaptic dopamine are thought to cause the craving for cocaine that is associated with its abuse (Dackis and Gold, *J. Substance Abuse Treatment 2*:139 (1985) and Kleber and Gawin, *Am. J. Drug Alcohol Abuse 12*:235 (1986)).

Agonists for the D1 dopamine receptor subtype have been shown to be effective in treating Parkinson's disease induced in laboratory animals (Kebabian *et al., Eur. J. Pharm. 229:*203 (1992), Taylor *et al., Eur. J. Pharm. 199:*389 (1991) and Michaelides *et al., J. Med. Chem. 38:*3445 (1995)). Similarly, recent studies have shown that antagonists and partial agonists for the D1 dopamine receptor subtype may be effective in treating cocaine abuse (Caine and Koob, *J. Pharm Exp. Ther. 270:*209 (1994) and Bergman and Rosenzweig-Lipson, *Problems of Drug Dependence,* 1991 NIDA Research Monograph 119, page 185 (1992)).

Therefore, there is a need for new compounds in new structural classes having selective activities for the D1 dopamine receptor.

## Summary of the Invention

It has now been found that Compounds 1 and 2 have the necessary pharmacophores in the regions of three dimensional space required for selective binding to the D1 dopamine receptor (Example 1). Thus, it is expected that these compounds will be selective D1 receptor agonists and their monohydroxy analogs will be partial D1 receptor agonist.

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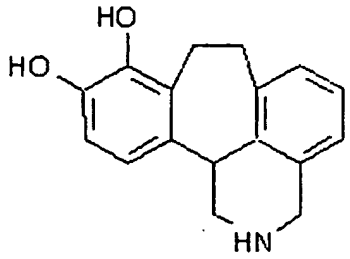
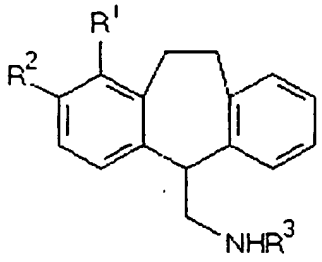



(2)

In one embodiment, the present invention is a compound represented by Structural Formula I:



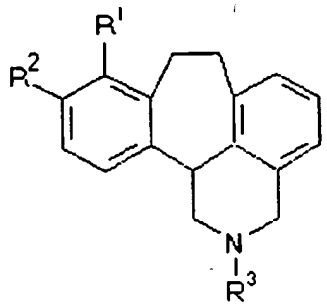

(I)

$R^1$ is selected from the group consisting of -OH and $-OR^4$, wherein $R^4$ is selected from the group consisting of a lower alkyl group, an alkylene group and a phenol protecting group.

$R^2$ is selected from the group consisting of -H, -OH, $-OR^5$ and a halogen, wherein $R^5$ is selected from the group consisting of a lower alkyl group, a phenol protecting group and $R^4$, when $R^4$ is an alkylene group.

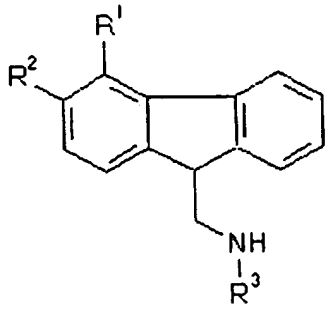
$R^3$ is selected from the group consisting of -H, an amine protecting group, a lower alkyl group and a lower alkyl group substituted with an aryl group. In one aspect, $R^3$ is selected from the group consisting -H and a lower alkyl group.

In another embodiment, the compound of the present invention is represented by Structural Formula II:



(II)

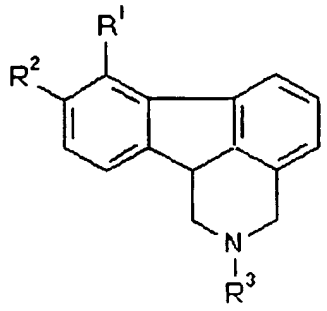
wherein $R^1$-$R^5$ are as defined above for Structural Formula I. In another embodiment, the compound of the present invention is represented by Structural Formula III:



(III)

wherein $R^1$-$R^5$ are as defined above by Structural Formula I.

In another embodiment, the compound of the present invention is represented by Structural Formula IV:



(IV)

wherein $R^1$-$R^5$ are as defined above for Structural Formula I.

Yet another embodiment of the present invention is a method of stimulating a D1 dopamine receptor in an individual. The method comprises administering to the individual a stimulatory amount of a compound represented by Structural Formulas I, II, III or IV.

Compounds **1** and **2** can be used to treat individuals with Parkinson's disease. The monohydroxy analogs of **1** and **2** can be used to treat individuals who abuse cocaine. In addition, these compounds are useful for molecular modeling in order to further define the required spatial orientation of the amine and hydroxy-substituted phenyl ring for binding to the D1 receptor. They can also be used as standards in *in vitro* binding assays for screening compounds for their ability to bind to the D1 receptor and for characterizing the effect of these kinds of compounds in the body.

Description of the Figures

Figures 1A and 1B represent the stereoscopic images of the superposition of the hydroxylated phenyl rings of the energy minimized compounds **1** and **2** (light lines) onto the energy minimized structure of the D1-selective full agonist dihydrexidine (dark lines).

Detailed Description of the Invention

The features and other details of the invention will now be more particularly described with reference to the accompanying examples and pointed out in the claims. It will be understood that the particular embodiments of the invention are shown by way of illustration and not as limitations of the invention. The principal features of this invention can be employed in various embodiments without departing from the scope of the invention.

"Stimulating" a D1 dopamine receptor (referred to herein as a "D1 receptor") refers to causing a molecule to bind, complex or interact with the D1 receptor so that the cellular activity which is affected or controlled by the D1 receptor either increases or decreases. For example, D1 agonists and antagonists, respectively, stimulate and inhibit the enzyme adenylate cyclase, which produces the cellular messenger cyclic adenosine monophosphate (AMP) (Clement-Cormrer *et al.*, *Proc. Natl. Acad. Sci. USA* 71:1113 (1974) and Stoof and Kebabian, *Nature* 294:366 (1981)). A compound which stimulates a D1 receptor can be an agonist, (i.e., a compound which causes the cellular activity affected or controlled by the D1 receptor to increase) or an antagonist (i.e., a compound which causes the cellular activity affected or controlled by the D1 receptor to decrease). A compound which stimulates a D1 receptor can also be a partial agonist (a mixed agonist/antagonist,

i.e., a compound which can act as either an agonist or an antagonist, depending on the tissue type).

A "stimulatory amount" of a compound, as used herein, is the quantity of a compound which, when administered to an individual, results in a discernable increase or decrease of cellular activity affected or controlled by the D1 receptor. Administration of a stimulatory amount of a compound typically causes an observable physiological response resulting from the increase or decrease in a cellular activity under the control of a D1 receptor (see, for example, Taylor *et al.*, *Eur. J. Pharm. 199:*389 (1991) and Kebabian *et al.*, *Eur. J. Pharm. 229:*203 (1995)). For example, D1 agonists can stimulate a bovine parathyroid gland to produce an increase in the release of parathyroid hormone (Brown *et al.*, *Proc. Natl. Acad. Sci. USA 74:*4210 (1977) and Brown *et al.*, *Mol. Pharm. 18:*335 (1980)). A "stimulatory amount" can also refer to the amount of compound which decreases or alleviates the symptoms of a disease involving the D1 receptor or a disease involving molecules, such as dopamine, which stimulate the D1 receptor, e.g. Parkinson's disease or cocaine abuse. Typically, a "stimulatory amount" of the compound ranges from about 1 mg/day to about 1000 mg/day.

Compounds of the invention which act as D1 receptor agonists can be used in a method of treating an individual afflicted with Parkinson's disease. The method comprises administering a therapeutically effective amount of the D1 receptor agonist to the individual afflicted with Parkinson's disease.

Compounds of the invention which are D1 receptor agonists are compounds represented by Structural Formulas I-IV, wherein $R^2$ is selected from the group consisting of -OH and $-OR^5$, and wherein $R^5$ is as defined above. Examples of compounds which can be used for the treatment of

Parkinson's disease include compounds represented by Structural Formulas II and IV, wherein $R^1$ and $R^2$ are each -OH and $R^3$ is -H. Other examples include compounds represented by Structural Formulas I and III, where $R^1$ and $R^2$ are each -OH and $R^3$ is -H or $-CH_3$.

Compounds of the invention which act as D1 receptor partial agonist can be used in a method for treating an individual who abuses cocaine. In this embodiment, the method of the invention comprises administering a therapeutically effective amount of the D1 receptor partial agonist to an individual who abuses cocaine.

Compounds of the invention which act as a D1 receptor partial agonist are compounds represented by Structural Formulas I-IV, wherein $R^2$ is -H or a halogen. Examples of compounds which can be used for the treatment of cocaine abuse include compounds represented by Structural Formulas II and IV, wherein $R^1$ is -OH and $R^2$ and $R^3$ are each -H. Other examples include compounds represented by Structural Formulas I and III, wherein $R^1$ is -OH, $R^2$ is -H and $R^3$ is -H or $-CH_3$.

A "therapeutically effective" amount of a compound is the amount of compound which decreases or alleviates the severity of the symptoms associated with a disease, e.g., Parkinson's disease or cocaine abuse, in an individual being treated with the compound. In the case of treatment of cocaine abuse, a "therapeutically effective" amount of a compound can be the amount of compound which decreases an addicted individual's craving for cocaine. Typically, a "therapeutically effective amount" of the compound ranges from about 1 mg/day to about 1000 mg/day.

As used herein, a "lower alkyl" group is a substituted or unsubstituted C1-C12 alkyl group, and can be straight-chained, branched or cyclic. A lower alkyl group can also include one or more units of unsaturation.

As used herein, an "aryl group" includes, for example, phenyl, substituted phenyl, heteroaryl (e.g. thienyl, furanyl, pyridinyl and benzothienyl) or substituted heteroaryl groups. Examples of suitable substituents on an aryl or heteroaryl group include -CN, $-NO_2$, halogen, lower alkyl, -OR, -NHR, and -SR, wherein R is a C1-C6 alkyl group or a protecting group for an alcohol, amine or thiol group. Examples of suitable halogens include chlorine, bromine and fluorine.

Alkylene groups can be used to form a bridge between two *ortho* phenolic oxygens, e.g., $R^3$ and $R^5$ in Structures I-IV, taken together, can form an alkylene group.

Examples of suitable "alkylene groups" include $-(CH_2)-$, $-(CH_2-CH_2)-$, -(CHX)-, -(CXY)-, $-(CHX-CH_2)-$ and -(CHX-CHY)-, wherein X and Y are C1-C4 alkyl groups and are independently chosen. A preferred alkylene group is methylene.

"Protecting group" has the definition commonly afforded to the term, namely a chemical moiety bonded to a functional group in a molecule, which is removable when exposed to suitable chemical reagent(s) or enzyme(s) to regenerate a free functional group.

Examples of suitable phenol and alcohol protecting groups include *t*-butyl, methoxymethyl, 2-tetrahydropyranyl, 2-tetrahydrofuranyl, -CO(lower alkyl), (lower alkyl)-O-C-, (lower alkyl) -NH-C-, -CO(aryl), silyl esters, (e.g. triisopropylsilyl and *t*-butyldimethyl silyl), trifluoracetate, 2-methoxyethoxy-methyl, siloxymethyl, benzyloxycarbonyl (BOC) and carboxycarbonyl (CBZ). Suitable amine protecting groups include *t*-butyloxycarbonyl (BOC), benzyloxycarbonyl (CBZ), 9-fluorenylmethoxycarbonyl (f-MOC), 2,2,2-trichloroethoxycarbonyl, 2-haloethoxy-

carbonyl, benzoyl, phthalimidyl, diphenylphosphinyl and benzensulfonyl. Other suitable phenol, alcohol, amine and thiol protecting groups are given in Greene, "Protecting Groups in Organic Synthesis," John Wiley and Sons, Second Edition, (1991), and are within the scope of the present invention.

The compounds of the present invention can be administered to an individual in the form of a pro-drug, i.e., the compound being administered is converted into the active agent *in vivo*. A pro-drug is often used to enhance certain desirable properties of the compound. For example, the pro-drug can have greater lipophilicity than the parent drug and, therefore, greater ability to cross the blood brain barrier. A pro-drug can also stabilize the pharmacologically active substance, e.g., by preventing metabolism of the pharmacologically active substance by, for example, oxidation.

The compounds of the present invention can be converted into pro-drugs by protecting the phenol(s) and/or amine functionalities with groups that are capable of being removed *in vivo*. For example, phenolic esters, carbonates and carbamates are degraded by cellular enzymes to yield phenols (Dittert *et al.*, *J. Pharm. Sci. 57:783 (1968)*, Dittert *et al.*, *J. Pharm. Sci.* 57:828 (1968), Dittert *et al.*, *J. Pharm. Sci. 58:*557 (1969) and Ratie *et al.*, *J. Pharm. Sci. 59:*1739 (1970)). Suitable, phenol protecting groups which can be removed *in vivo* to regenerate the free phenol, include (C1-C8 alkyl)-$\overset{O}{\overset{\|}{C}}$O-, (C1-C8 alkyl)-O-$\overset{O}{\overset{\|}{C}}$- and (C1-C8 alkyl)-NH-$\overset{O}{\overset{\|}{C}}$-. Also included is when the phenols are protected in the form a methylene dioxy group. In addition, a variety of carbamate groups used to protect

amines are known to undergo spontaneous cleavage in solution at kinetically favorable rates (Saari, *et al. J. Med. Chem.*, *33*:97 (1990)) and would thus be expected to degrade *in vivo*. Carbamates are also degraded enzymatically, (King, *et al.*, *Biochemistry, 26*:2294 (1987)), particularly in blood (Tunek, *et al.*, *Biochemical Pharmacology, 37*:3867 (1988)) to afford an unprotected amine. Suitable amine protecting groups which are removable *in vivo* include phenyl-O-C(=O)- and (C1-C6 alkyl substituted phenyl)-O-C(=O)- and (C1-C3 alkoxy substituted phenyl)-O-C(=O)-.

The compounds of the present invention can be administered by a variety of known methods, including orally, rectally, or by parenteral routes (e.g., intramuscular, intravenous, subcutaneous, nasal or topical). The form in which the compounds are administered will be determined by the route of administration. Such forms include, but are not limited to capsular and tablet formulations (for oral and rectal administration), liquid formulations (for oral, intravenous, intramuscular or subcutaneous administration) and slow releasing microcarriers (for rectal, intramuscular or intravenous administration). The formulations can also contain a physiologically acceptable vehicle and optional adjuvants, flavorings, colorants and preservatives. Suitable physiologically acceptable vehicles may include saline, sterile water, Ringer's solution, and isotonic sodium chloride solutions. The specific dosage level of active ingredient will depend upon a number of factors, including,

for example, biological activity of the particular preparation, age, body weight, sex and general health of the individual being treated.

The compounds of the present invention used in the treatment of an individual with Parkinson's disease can be co-administered with other pharmaceutically active agents used in the treatment of Parkinson's disease. The compounds of the present invention used in the treatment of an individual who abuses cocaine can be combined with other therapies used to treat individuals who abuse cocaine. Such therapies can include the co-administration of other pharmaceutically active agents used to treat cocaine abuse or psychological therapies.

When the compounds of the present invention are used in combination with other pharmaceutically active agents, the specific combination will vary, depending on a number of factors, including, for example, activity of the agents, their side-effects, and the weight, age, sex and general health of the individual being treated.

The preparation of compounds of the present invention are shown in Schemes 1 and 2 and described more fully in Examples 2 and 3.

The invention is further illustrated by the following examples, which are not intended to be limiting in any way.

Example 1 - Energy Minimization Studies on Compounds 1 and 2

Energy minimization studies were performed on Compounds **1** and **2**.

The energy minimized structures of **1** and **2** have been superimposed onto the energy minimized conformation of the

active enantiomer of dihydrexidine (Knoerzer *et al.*, *J. Med. Chem.* *37*:2453 (1994)), as shown in Figures 1A and 1B. Dihydrexidine is a known D1 selective agonist.

Compounds **1** and **2** present similar nonplanar pharmacophores with the amine group and phenyl rings placed in similar regions of three dimensional space, as in dihydrexidine and other D1 selective compounds (Froimowitz and Bellott, *J. Mol. Model.* *1*:36 (1995)).

Calculations of the conformational flexibilities of **1** and **2** were performed and compared with that of dihydrexidine. These studies show that in dihydrexidine, one phenyl ring can be either above or below the plane of the other, due to close contacts between the phenyl rings (Fromowitz and Bellott, *J. Mol. Model.* *1*:36 (1995)). Both conformers were energy minimized with the result that the conformer shown in Figures 1A and 1B is preferred by 1.5 kcal/mole. This is also the conformer observed in the crystal state of a dihydrexidine analog (Knoerzer *et al.* 1994).

These results also indicate that Compounds **1** and **2** have two possible conformations of the two-carbon link between the phenyl rings and that there is a substantial energy difference (3.4 kcal/mole for **2**) between these two conformers. Compound **1**, as with other nonplanar tricyclic structures, has additional flexibility in that the tricyclic structure can invert (Froimowitz and Ramsby, *J. Med. Chem.* *34*:1707 (1991)) and the preferred folding will be the one in which the side chain is pseudoequatorial. In addition, the amine-containing side chain can be conformationally *trans* to either phenyl ring and there is little energy difference between these possibilities due to the near symmetry of the molecule. Compound **2** is a less

flexible analog of **1** and the ammonium hydrogens are similarly placed to those in dihydrexidine.

The monohydroxy analog of the D1 receptor agonist dihydrexidine is a partial D1 agonist (Seiler *et al., J. Med. Chem. 36*:977 (1993)). In addition, the same modification to the catechol-containing partial agonist apomorphine produces a D1 antagonist (Schaus *et al J. Med. Chem. 33*:600 (1990). Thus, it is expected that the monohydroxy analog of **1** and **2** will result in a D1 partial agonist or antagonist.

Energy minimization of the compounds in this study were performed with respect to all internal coordinates using the MM2-87 program and parameter set of Allinger and Yuh, *Quantum Chem. Program Exch. 12*:program 395 (1980). All calculations were performed for the protonated molecule. Initial Cartesian coordinates of the molecules were generated with PCMODEL program (Serena Software, Box 3076, Bloomington, IN 47402-3076) or the DRIVER option of the MM2-87 program. The dielectric constant was set to 80 and the hydrogen bonding terms involving the ammonium group were set to zero to approximate a water solution and to prevent intramolecular electrostatic forces from dominating the calculations in the absence of explicit water molecules (Froimowitz, *J. Comput. Chem. 14*:934 (1993) and Froimowitz *et al., J. Med. Chem. 36*:2219 (1993)). To ensure complete convergence of the calculations, the convergence criteria was set to 1/8 of its default.

Example 2 - Synthesis of Compound 1

The preparation of the dimethoxybenzalphthalide **8** is carried out by reaction of 2,3-dimethoxyphenylacetic acid **4** with phthalic anhydride **6** in the presence of sodium acetate

(Weiss, Organic synthesis, Collective Volume II, page 61). Catalytic reduction (Raney nickel/hydrogen) of the dimethoxybenzalphthalide **8** yields the phenethylbenzoic acid **10**. Cyclization of the phenethylbenzoic acid **10** with polyphosphoric acid yields the cycloheptadienone **12** (Winthrop *et al., J. Org. Chem. 27*:230 (1962)).

Condensation of the cycloheptadienone **12** with nitromethane yields the nitroalkane **14**, which is catalytically hydrogenated to produce compound **16**. Chiral resolution of the racemate is carried out by HPLC with a chiral column such as CHIRACEL OD (J.T. Baker) (Froimowitz *et al., Drug Design and Discovery 13*:73 (1995)). Demethylation of each enantiomer with $BBr_3$ or HBr provides the final optically pure product **1**.

Alkyl groups are introduced onto the amine by reductive alkylation (Gribble *et al., J. Am. Chem. Soc., 96*:7812 (1974)).

Example 3- Synthesis of Compound 2

To prevent cyclization to the activated benzo ring, the aryl hydrogens of the activated benzo ring of the cycloheptadienone **12** are protected by electrophilic dibromination with $Br_2$ to give the cycloheptadienone **18**. The carbonyl group of the cycloheptadienone **18** is converted to a methylamino group by successive reduction with $NaBH_4$, alcohol tosylation, displacement with cyanide and reduction to produce compound **20**. The benzocyclo-heptatriene-isoquinoline ring system is then produced according to literature methods (Humber *et al., J. Heterocyclic Chem. 3*:247 (1966)) to afford lactam **22**. Reduction of lactam **22** with lithium aluminum hydride effects the reduction of the

lactam functionality and the reductive debromination of the protecting halogens to produce compound **24**. Chiral resolution is carried out as described in Example 1. Demethylation is then accomplished with $BBr_3$ or HBr to give **2**.

Example 4 - Binding Assay for the D1 Receptor

The binding assay for the D1 receptor utilizes homogenized rat striatal membrane preparations. An $IC_{50}$ curve is generated from 10 concentrations of the test compound ($10^{-10}$ to $10^{-5}$ M) performed in duplicate using the LIGAND program for data analysis (Munson and Rodbard, *Anal. Biochem. 107*:220 (1980)). Binding is assessed by filtering incubates on polyethylenimine-presoaked Whatman GF/B filters and by scintillation counting (Billard *et al.*, *Life Sci. 35*:1885 (1984)). The radioactive ligand is $^3$H SCH-23390 at a concentration of 0.3 nM and the buffer consists of 50 mM Tris-HCl (pH 7.4), 120 mM KCl, 2 mM $CaCl_2$ and 1 mM $MgCl_2$ (Billard *et al.*, *Life Sci. 35*:1885 (1984)). Incubation time is fifteen minutes at 37°C. Non-specific binding is defined with 1 μM (+)-butaclamol.

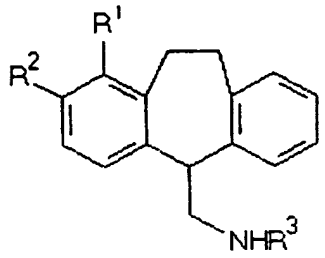
Equivalents

Those skilled in the art will know, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. These and all other equivalents are intended to be encompassed by the following claims.

CLAIMS

What is claimed is:

1. A compound represented by the following structural formula:




wherein:

$R^1$ is selected from the group consisting of -OH and $-OR^4$, wherein $R^4$ is selected from the group consisting of a lower alkyl group, an alkylene group and a phenol protecting group;

$R^2$ is selected from the group consisting of -H, -OH, $-OR^5$ and a halogen, wherein $R^5$ is selected from the group consisting of a lower alkyl group, a phenol protecting group and $R^4$, when $R^4$ is an alkylene group; and

$R^3$ is selected from the group consisting of -H, an amine protecting group, a lower alkyl group and a lower alkyl group substituted with an aryl group.

2. The compound of Claim 1 wherein:

a) $R^1$ and $R^2$ are each -OH; and

b) $R^3$ is -H or $-CH_3$.

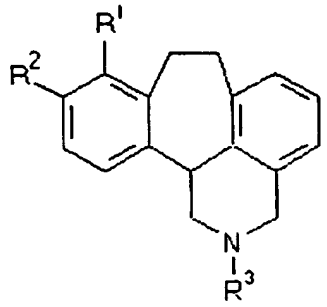
3. The compound of Claim 1 wherein:

a) $R^1$ is -OH;

b) $R^2$ is -H; and

c) $R^3$ is -H or $-CH_3$.

4. A compound represented by the following structural formula:




wherein:

$R^1$ is selected from the group consisting of -OH and $-OR^4$, wherein $R^4$ is selected from the group consisting of a lower alkyl group, an alkylene group and a phenol protecting group;

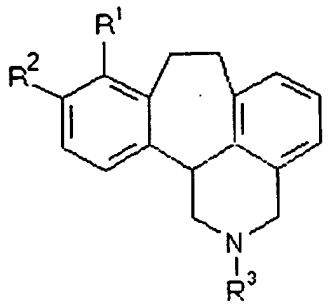
$R^2$ is selected from the group consisting of -H, -OH, $-OR^5$ and a halogen, wherein $R^5$ is selected from the group consisting of a lower alkyl group, a phenol protecting group and $R^4$, when $R^4$ is an alkylene group;

$R^3$ is selected from the group consisting of -H, an amine protecting group, a lower alkyl group and a lower alkyl group substituted with an aryl group.

5. The compound of Claim 4 wherein:
   a) $R^1$ and $R^2$ are each -OH; and
   b) $R^3$ is -H.

6. The compound of Claim 4 wherein:
   a) $R^1$ is -OH; and
   b) $R^2$ and $R^3$ are each -H.

7. A method of treating an individual who abuses cocaine, comprising administering a therapeutically effective amount of a compound represented by the following structural formula:




wherein:

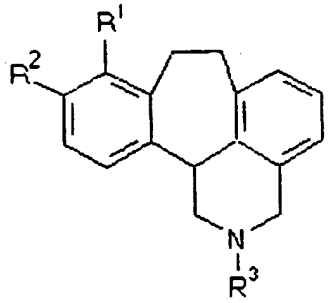
$R^1$ is selected from the group consisting of -OH and -$OR^4$, wherein $R^4$ is selected from the group consisting of a lower alkyl group and a phenol protecting group;

$R^2$ is selected from the group consisting of -H and a halogen; and

$R^3$ is selected from the group consisting of -H, an amine protecting group, a lower alkyl group and a lower alkyl group substituted with an aryl group.

8. The method of Claim 7 wherein:
   a) $R^1$ is -OH; and
   b) $R^2$ and $R^3$ are each -H.

9. A method of treating an individual who abuses cocaine, comprising administering a therapeutically effective amount of a compound represented by the following structural formula:




wherein:

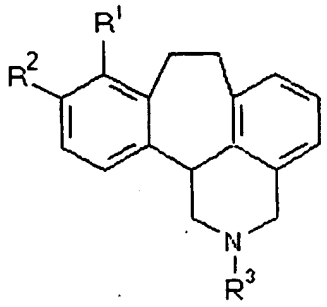
$R^1$ is selected from the group consisting of -OH and $-OR^4$, wherein $R^4$ is selected from the group consisting of a lower alkyl group and a phenol protecting group;

$R^2$ is selected from the group consisting of -H and a halogen; and

$R^3$ is selected from the group consisting of -H, an amine protecting group, a lower alkyl group and a lower alkyl group substituted with an aryl group.

10. The method of Claim 9 wherein:
   a) $R^1$ is -OH; and
   b) $R^2$ and $R^3$ are each -H.

11. A method of treating an individual with Parkinson's disease comprising administering to the individual a therapeutically effective amount of a compound represented by the following structural formula:



wherein:

$R^1$ is selected from the group consisting of -OH and $-OR^4$, wherein $R^4$ is selected from the group consisting of a lower alkyl group, an alkylene group and a phenol protecting group;

$R^2$ is selected from the group consisting of -OH and $-OR^5$, wherein $R^5$ is selected from the group consisting of a lower alkyl group, a phenol protecting group and $R^4$, when $R^4$ is an alkylene group;

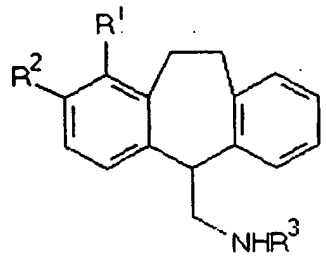
$R^3$ is selected from the group consisting of -H, an amine protecting group, a lower alkyl group and a lower alkyl group substituted with an aryl group.

12. The method of Claim 11 wherein:

a) $R^1$ and $R^2$ are each -OH; and

b) $R^3$ is -H.

13. A method of treating an individual with Parkinson's Disease comprising administering to the individual a therapeutically effective amount of a compound represented by the following structural formula:




wherein:

$R^1$ is selected from the group consisting of -OH and $-OR^4$, wherein $R^4$ is selected from the group consisting of a lower alkyl group, an alkylene group and a phenol protecting group;

$R^2$ is selected from the group consisting of -OH and $-OR^5$, wherein $R^5$ is selected from the group consisting of a lower alkyl group, a phenol protecting group and $R^4$, when $R^4$ is an alkylene group;

$R^3$ is selected from the group consisting of -H, an amine protecting group, a lower alkyl group and a lower alkyl group substituted with an aryl group.

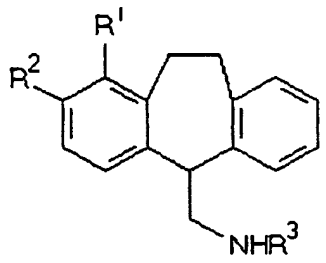
14. The method of Claim 13 wherein:

a) $R^1$ and $R^2$ are each -OH; and

b) $R^3$ is -H or $-CH_3$.

15. A method of stimulating a D1 dopamine receptor in an individual, comprising administering to the individual

a stimulatory amount of a compound represented by the following structural formula:



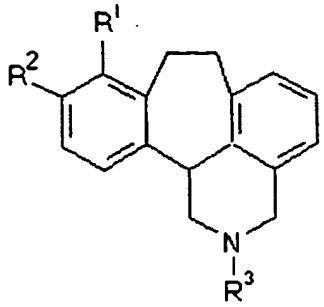

wherein:

$R^1$ is selected from the group consisting of -OH and $-OR^4$, wherein $R^4$ is selected from the group consisting of a lower alkyl group, an alkylene group and a phenol protecting group;

$R^2$ is selected from the group consisting of -H, -OH, $-OR^5$ and a halogen, wherein $R^5$ is selected from the group consisting of a lower alkyl group, a phenol protecting group and $R^4$, when $R^4$ is an alkylene group; and

$R^3$ is selected from the group consisting of -H, an amine protecting group, a lower alkyl group and a lower alkyl group substituted with an aryl group.

16. A method of stimulating a D1 dopamine receptor in an individual, comprising administering to the individual a stimulatory amount of a compound represented by the following structural formula:



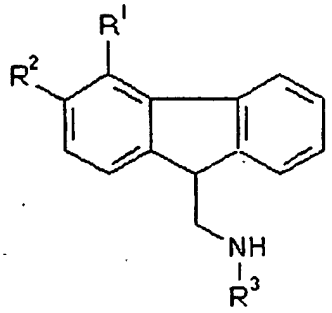
wherein:

$R^1$ is selected from the group consisting of -OH and $-OR^4$, wherein $R^4$ is selected from the group consisting of a lower alkyl group, an alkylene group and a phenol protecting group;

$R^2$ is selected from the group consisting of -H, -OH, $-OR^5$ and a halogen, wherein $R^5$ is selected from the group consisting of a lower alkyl group, a phenol protecting group and $R^4$, when $R^4$ is an alkylene group; and

$R^3$ is selected from the group consisting of -H, an amine protecting group, a lower alkyl group and a lower alkyl group substituted with an aryl group.

17. A compound represented by the following structural formula:



wherein:

$R^1$ is selected from the group consisting of -OH and $-OR^4$, wherein $R^4$ is selected from the group consisting of a lower alkyl group, an alkylene group and a phenol protecting group;

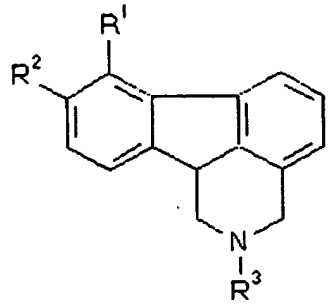
$R^2$ is selected from the group consisting of -H, -OH, $-OR^5$ and a halogen, wherein $R^5$ is selected from the group consisting of a lower alkyl group, a phenol protecting group and $R^1$, when $R^4$ is an alkylene group; and

$R^3$ is selected from the group consisting of -H, an amine protecting group, a lower alkyl group and a lower alkyl group substituted with an aryl group.

18. The compound of Claim 17 wherein:
a) $R^1$ and $R^2$ are each -OH; and
b) $R^3$ is -H or $-CH_3$.

19. The compound of Claim 17 wherein:
a) $R^1$ is -OH;
b) $R^2$ is -H; and
c) $R^3$ is -H or $-CH_3$.

20. A compound represented by the following structural formula:



wherein:

$R^1$ is selected from the group consisting of -OH and $-OR^4$, wherein $R^4$ is selected from the group consisting of a lower alkyl group, an alkylene group and a phenol protecting group;

$R^2$ is selected from the group consisting of -H, -OH, $-OR^5$ and a halogen, wherein $R^5$ is selected from the group consisting of a lower alkyl group, a phenol protecting group and R', when $R^4$ is an alkylene group; and

$R^3$ is selected from the group consisting of -H, an amine protecting group, a lower alkyl group and a lower alkyl group substituted with an aryl group.

21. The compound of Claim 20 wherein:

a) $R^1$ and $R^2$ are each -OH; and

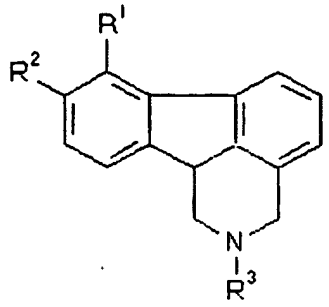
b) $R^3$ is -H.

22. The compound of Claim 20 wherein:

a) $R^1$ is -OH; and

b) $R^2$ and $R^3$ are each -H.

23. A method of treating an individual who abuses cocaine, comprising administering a therapeutically effective amount of a compound represented by the following structural formula:



wherein:

$R^1$ is selected from the group consisting of -OH and $-OR^4$, wherein $R^4$ is selected from the group consisting of a lower alkyl group and a phenol protecting group;

$R^2$ is selected from the group consisting of -H and a halogen; and

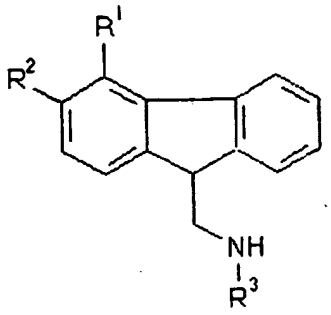
$R^3$ is selected from the group consisting of -H, an amine protecting group, a lower alkyl group and a lower alkyl group substituted with an aryl group.

24. The method of Claim 23 wherein:

a) $R^2$ is -OH; and

b) $R^2$ and $R^3$ are each -H.

25. A method of treating an individual who abuses cocaine, comprising administering a therapeutically effective amount of a compound represented by the following structural formula:




wherein:

$R^1$ is selected from the group consisting of -OH and $-OR^4$, wherein $R^4$ is selected from the group consisting of a lower alkyl group and a phenol protecting group;

$R^2$ is selected from the group consisting of -H and a halogen; and

$R^3$ is selected from the group consisting of -H, an amine protecting group, a lower alkyl group and a lower alkyl group substituted with an aryl group.

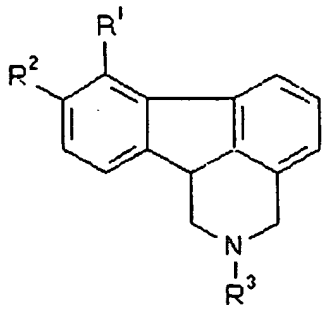
26. The method of Claim 25 wherein:

a) $R^1$ is -OH;

b) $R^2$ is -H; and

c) $R^3$ is -H or $-CH_3$.

27. A method of treating an individual with Parkinson's Disease comprising administering to the individual a therapeutically effective amount of a compound represented by the following structural formula:



wherein:

$R^1$ is selected from the group consisting of -OH and $-OR^4$, wherein $R^4$ is selected from the group consisting of a lower alkyl group, an alkylene group and a phenol protecting group;

$R^2$ is selected from the group consisting of -OH and $-OR^5$, wherein $R^5$ is selected from the group consisting of a lower alkyl group, a phenol protecting group and $R^4$, when $R^4$ is an alkylene group; and

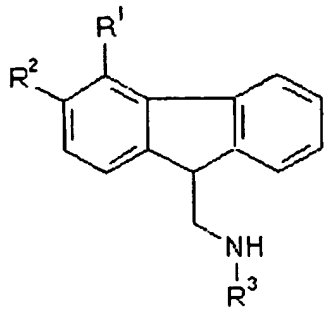
$R^3$ is selected from the group consisting of -H, an amine protecting group, a lower alkyl group and a lower alkyl group substituted with an aryl group.

28. The method of Claim 27 wherein:

a) $R^1$ and $R^2$ are each -OH; and

b) $R^3$ is -H.

29. A method of treating an individual with Parkinson's Disease comprising administering to the individual a therapeutically effective amount of a compound represented by the following structural formula:




wherein:

$R^1$ is selected from the group consisting of -OH and $-OR^4$, wherein $R^4$ is selected from the group consisting of a lower alkyl group, an alkylene group and a phenol protecting group;

$R^2$ is selected from the group consisting of -OH and $-OR^5$, wherein $R^5$ is selected from the group consisting of a lower alkyl group, a phenol protecting group and $R^4$, when $R^4$ is an alkylene group; and

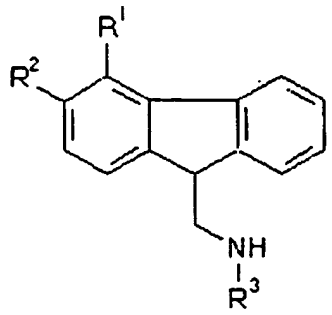
$R^3$ is selected from the group consisting of -H, an amine protecting group, a lower alkyl group and a lower alkyl group substituted with an aryl group.

30. The method of Claim 29 wherein:

a) $R^1$ and $R^2$ are each -OH; and

b) $R^3$ is -H or $-CH_3$.

31. A method of stimulating a D1 dopamine receptor in an individual, comprising administering to the individual a stimulatory amount of a compound represented by the following structural formula:



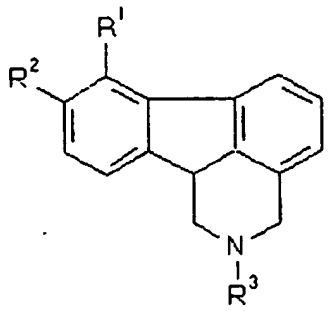
wherein:

$R^1$ is selected from the group consisting of -OH and $-OR^4$, wherein $R^4$ is selected from the group consisting of a lower alkyl group, an alkylene group and a phenol protecting group;

$R^2$ is selected from the group consisting of -H, -OH, $-OR^5$ and a halogen, wherein $R^5$ is selected from the group consisting of a lower alkyl group, a phenol protecting group and $R^6$, when $R^6$ is an alkylene group; and

$R^3$ is selected from the group consisting of -H, an amine protecting group, a lower alkyl group and a lower alkyl group substituted with an aryl group.

32. A method of stimulating a D1 dopamine receptor in an individual, comprising administering to the individual a stimulatory amount of a compound represented by the following structural formula:



wherein:

$R^1$ is selected from the group consisting of -OH and $-OR^4$, wherein $R^4$ is selected from the group consisting of a lower alkyl group, an alkylene group and a phenol protecting group;

$R^2$ is selected from the group consisting of -H, -OH, $-OR^5$ and a halogen, wherein $R^5$ is selected from the group consisting of a lower alkyl group, a phenol protecting group and $R^4$, when $R^4$ is an alkylene group; and

$R^3$ is selected from the group consisting of -H, an amine protecting group, a lower alkyl group and a lower alkyl group substituted with an aryl group.

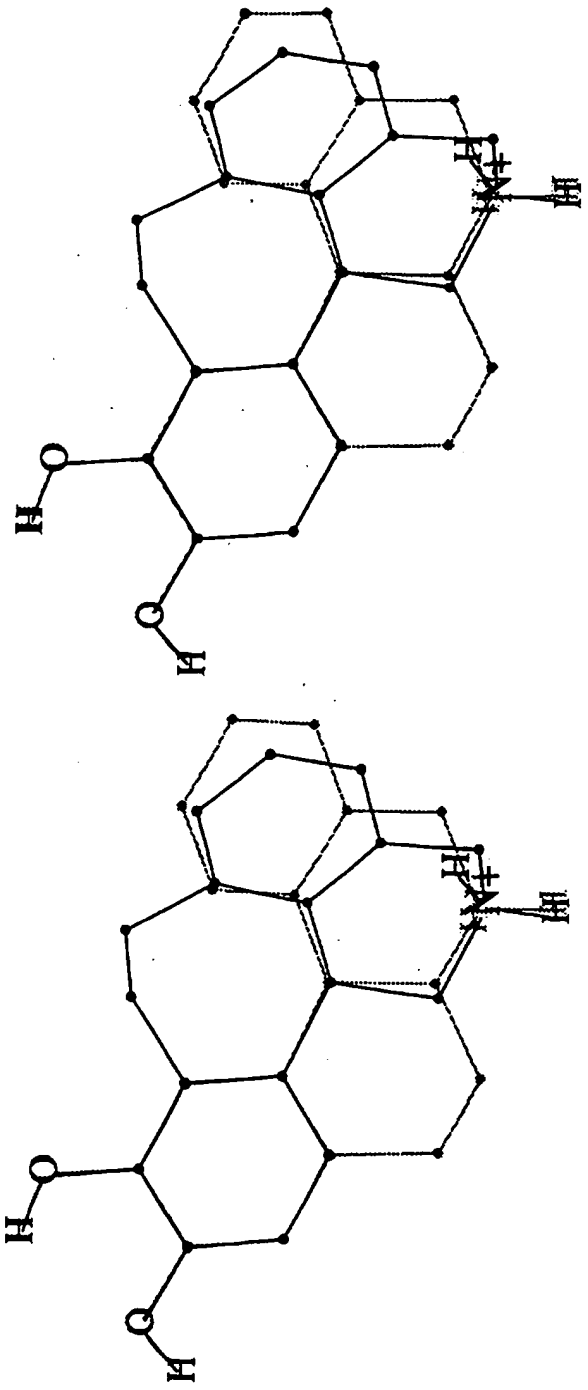


Figure 1A

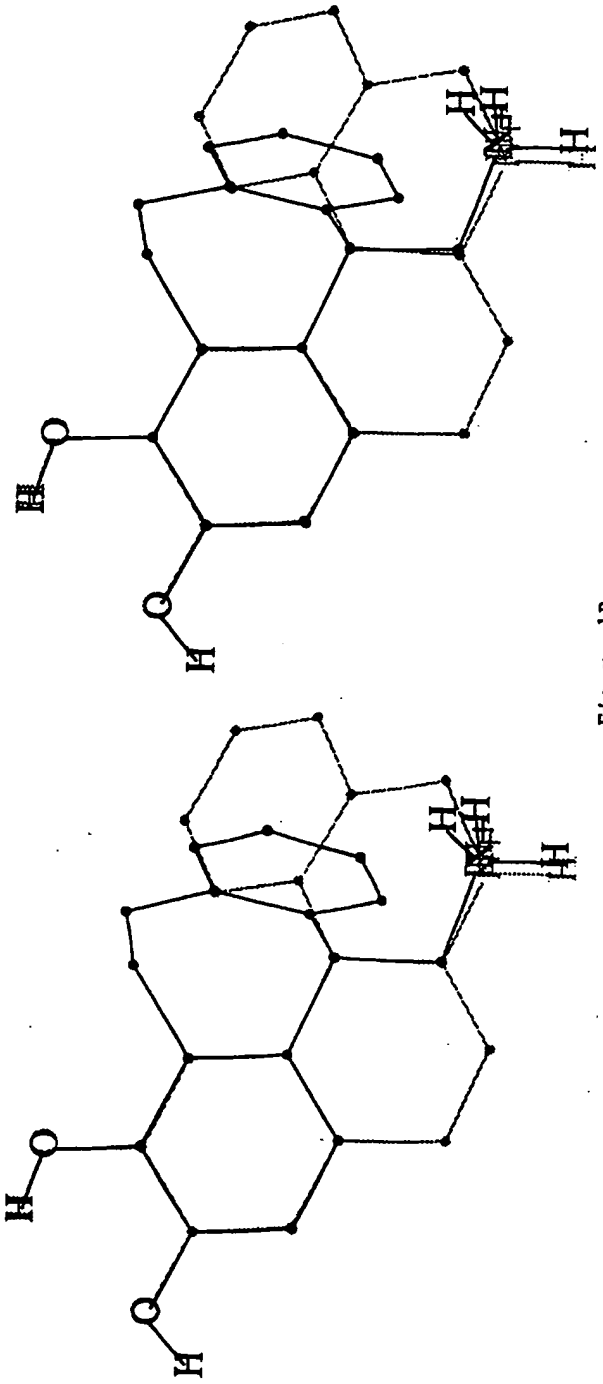


Figure 1B

# INTERNATIONAL SEARCH REPORT

Inte .onal Application No
PCT/US 97/02620

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D221/18 C07C215/64 C07C217/74 A61K31/44 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | JOURNAL OF MEDICINAL CHEMISTRY, vol. 29, no. 10, October 1986, WASHINGTON US, pages 1904-1912, XP002031848 DAVID L.LADD ET AL: "Synthesis and dopaminergic binding of 2-Aryldopamine analogues:Phenethylamines,3-Benzazepines,and 9-(aminomethyl)fluorenes" see page 1908,compounds 33a,33b,4a,4b and experimental section and page 1912 --- | 17-19, 25,26, 29-31 |
| A | WO 90 12574 A ( NORTHEASTERN UNIVERSITY) 1 November 1990 see claims --- | 1-32 |
| A | US 3 992 445 A (ENGELHARDT EDWARD L) 16 November 1976 see the whole document --- | 1-32 |
| | -/-- | |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 29 May 1997 | 05. 06. 97 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016 | Henry, J |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 97/02620

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, no. 13, June 1995, WASHINGTON US, pages 2395-2408, XP002031849 SCOTT E.SNYDER ET AL: "Synthesis and evaluation of 6,7-dihydroxy-2,3,4,8,9,13b-hexahydro-1H-benzo[6,7]cyclohepta[1,2,3-ef][3]benzazepine,6,7-dihydroxy-1,2,3,4,8,12b-hexahydroanthr[10,4a,4cd]azepine,and 10-(aminomethyl)-9,10-dihydro-1,2-dihydroxyanthracene as conformationally restricted analogs of beta-phenyldopamine" see the whole document ----- | 1-32 |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/02620

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 7-16, 23-32 are directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/US 97/02620

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9012574 A | 01-11-90 | NONE | |
| US 3992445 A | 16-11-76 | NONE | |